REMARKS

Claims 31-33, 36-41, and 44-50 are currently pending in this application. Applicants, solely in an effort to expedite prosecution, have cancelled claims 34-35, 42 and 43. Applicants reserve the right to file continuations and/or divisionals directed to the subject matter of these cancelled claims. Applicants add claims 48-50. Support for these claims may be found in claims 35 and 42, and pages 8 and 27 of the specification. No new matter has been introduced by this amendment.

Applicants request Rejoinder of claims 44, 46 and 47. Under MPEP § 821.04, if applicants elect claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. Applicants assert that product claim 31 (and all other pending claims) is allowable and because the subject matter of claims 46 and 47 pertains to the same scope as the allowable claims in compliance with §821.04, these claims should be rejoined and allowed. In addition, because the elected species of claim 43 (now claim 49) is allowable, claim 44 should be rejoined.

I. Claim Objections Under 37 CFR § 1.75(c)

Claim 35 has been cancelled and claim 48 added in substitution to correct the assertion that claim 35 did not further limit the subject matter of the previous claim.

Applicants request that the objection to claim 41 (and 39) be held in abeyance until allowable subject matter is determined and the species election is finalized.

II. Claim Rejections Under 35 U.S.C. §112

A. Claims 39 and 41 have been rejected as lacking enablement because the assurances necessary to comply with deposit requirements have not been made.

Applicants' representative hereby states that the deposit of HB-12699 and HB-12700 was made under the terms of the Budapest Treaty on April 29, 1999, and, upon issuance of a patent from this application, all restrictions imposed upon the deposit will be irrevocably

removed, except the requirement that the Depository notify the patentee of a request for the deposited material. A copy of the Patent Deposit Receipt from the ATCC is enclosed. In view of this statement, Applicant requests that the rejection be withdrawn.

B. Claim 42 has been rejected as lacking written description. Solely in an effort to expedite prosecution, Applicants have cancelled claim 42 rendering this rejection moot.

C. Claim 43 has been rejected as lacking enablement. Solely in an effort to expedite prosecution, Applicants have cancelled claim 42 rendering this rejection moot.

New claim 49 has been added in substitution of claim 43. Applicants assert that the rejection of claim 43 should not apply to claim 49. Affinity maturation of antibodies is a common practice in the art and it would not require undue experimentation for a skilled artisan to perform modifications of the CDRs to obtain functional variants of SEQ ID NO 15-20.

D. Claims 31-33, 37-38, 40 And 45 have been rejected as lacking enablement because of the assumption raised by claim 34. Applicants amend claim 31 and cancel claim 34 in order to expedite prosecution. Therefore, Applicants request that the rejection be withdrawn.

E. Claim 38 has been rejected as lacking enablement because it claims fragments that are monovalent in nature. Applicants submit that the fragments of claim 38 are useful because after administration, more than one fragment may bind to the receptor resulting in dimerization. Therefore, Applicant request that the rejection be withdrawn.

III. Claim Rejections Under 35 U.S.C. §102

A. Claims 31-38, 40 and 45 have been rejected as anticipated by Cunningham et al. (U.S. Pat. No. 5,506,107). The Office asserts that "Cunningham et al disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands", and that "production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12, line 56." (Office Action dated Mar 29, 2005 at page 8).

Applicants respectfully traverse this rejection. First, in an Office Action dated January 9, 2001, in the parent application U.S. Appl. No. 09/303,155, the present Examiner admitted that this reference did not disclose any anti-GCSF agonist antibodies. Rather Cunningham et al. disclose merely a desire to make such antibodies, but do not provide the necessary disclosure to render the claimed invention anticipated. There are no examples of actual antibodies made to G-CSF. Applicants submit that this reference does not provide sufficient enablement to qualify as an anticipatory reference by the mere disclosure at column 12, line 56.

Skilled artisans know that it is relatively easy to obtain a neutralizing antibody because one merely blocks binding of the ligand, i.e. the G-CSF protein, to the receptor. However, an agonist antibody must bind to the receptor in a proper confirmation and trigger the activation of the receptor in the same manner as the native ligand. In the attached reference by Schneider et al. titled "Homodimerization of Erythropoietin Receptor by a Bivalent Monoclonal Antibody Triggers Cell Proliferation and Differentiation of Erythroid Precursors" the authors in their discussion at page 480 pose the question "Why are agonist antibodies to EPO-R so rare?", highlighting the difficulties in obtaining such agonist antibodies. The authors predicted that "all MoAbs specific to the extracellular domain should dimerize the receptor because they are bivalent." (page 480, last paragraph.) However, 47 out of 48 of their antibodies were not agonists. Prior to this, the authors stated, no agonist antibodies of EPO-R had been described. They concluded that the reason that so few agonists could be isolated was that the "cell surface imposes steric constraints and the two receptor subunits in the 2:1 complex have to be at a specific orientation and/or distance relative to each other." In view of this disclosure by Schneider et al. regarding EPO receptor agonists (EPO, HgH and G-CSF being in the same family) it is clear that a mere disclosure by Cunningham is not enabling for making agonist antibodies to G-CSF.

In addition, the present inventors discovered that in their own search for agonist antibodies, they found that using the D4 cell line expressing an artificial G-CSF receptor, similar in nature to that used by Cunningham, was not sufficiently predictive of a true agonist. As seen in Figure 5B of our application, MAb174-12 (solid triangles) appears to be an agonist antibody based on the amount of uptake of MTT as compared to the native G-CSF (solid squares). However, when this same antibody was tested in a colony-formation assay using human bone marrow cells (an assay that more closely mimics a true environment of cells with native human G-CSF receptor) it showed no agonist activity. This clearly shows that the screen described by Cunningham would not be sufficiently predictive for isolating agonist antibodies.

In view of the foregoing discussion, Applicants submit that Cunningham does not anticipate the claimed invention and the rejection should be withdrawn.

B. Claims 31-38, 40 and 45 have been rejected as anticipated by Adams et al. (U.S. Pat. No. 6,342,220). The Office asserts that "Adams et al disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands", and that "production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12, line 56." (Office Action dated Mar 29, 2005 at page 8).

Applicants respectfully traverse this rejection. Adams et al. do not disclose making or any examples of G-CSF agonist antibodies. The only disclosure at column 12 is a definition of cytokines and a list of examples. There is no disclosure of making agonist antibodies to G-CSF. The only other reference to G-CSF that the undersigned found was at column 24, line 53, and column 38, line 22, referring to the treatment of a mammal with an antibody in combination with a cytokine, e.g., G-

CSF, but no reference to making agonist antibodies to G-CSF. This reference only discloses the making of agonist antibodies to c-mpl.

Moreover, for all of the reasons set forth in Section A above, this reference does not enable the making of agonist antibodies to G-CSF. Therefore, Applicants submit that this reference does not anticipate the claimed invention and should be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the application is currently in condition for allowance and request a Notice of same.

Respectfully Submitted

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